O^2-SUBSTITUTED 1-[(2-CARBOXYLATO)PYRROLIDIN-1-YL] DIAZEN-1-IUM-1,2-DIOLATES

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

This application is a divisional of U.S. patent application Ser. No. 10/337,495, filed Jan. 7, 2003, now U.S. Pat. No. 6,911,433. which is a divisional of U.S. patent application Ser. No. 09/254,301, filed May 3, 1999, now U.S. Pat. No. 6,610,660, which is a U.S. national phase of International Patent Application No. PCT/US97/17267, filed Sep. 26, 1997, which claims the benefit of U.S. Provisional Patent Application No. 60/051,696, filed Jul. 3, 1997, U.S. Provisional Patent Application No. 60/045,917, filed May 7, 1997, and U.S. Provisional Patent Application No. 60/026,816, filed Sep. 27, 1996.

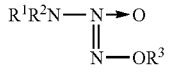
TECHNICAL FIELD OF THE INVENTION

The present invention relates to O^2-aryl 1-substituted diazen-1-ium-1,2-diolates (O^2-aryl diazeniumdiolates) O^2-glycosylated 1-substituted diazeniumdiolates, and O^2-substituted 1-[(2-carboxylato)pyrrolidin-1-yl]diazeniumdiolates, compositions comprising such diazeniumdiolates, methods of using such diazeniumdiolates, and methods of preparing O^2-aryl diazeniumdiolates.

BACKGROUND OF THE INVENTION

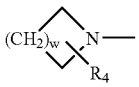
Nitric oxide (NO) has been implicated in a wide variety of bioregulatory processes, and compounds, which contain nitric oxide or are capable of releasing nitric oxide, have been identified as useful in regulating these processes. Many classes of nitric oxide-containing and/or releasing adducts are known in the art, such as glyceryl trinitrate and nitroprusside (reviewed in U.S. Pat. No. 5,405,919 (Keefer et al.), including limitations of their use in biological applications). The limited utility of such compounds has, in part, given rise to the development of another class of nitric oxide-generating compounds, diazeniumdiolates, which are especially useful biologically.

Diazeniumdiolates include compounds containing an $N_2O_2^-$ functional group and are structurally and functionally distinct from nitrosamines (see, e.g., Reilly, U.S. Pat. No. 3,153,094). The known diazeniumdiolates are disclosed in recently issued patents. U.S. Pat. No. 5,039,705 (Keefer et al.) and U.S. Pat No. 5,208,233 (Keefer et. al.) disclose secondary amine-nitric oxide adducts and salts thereof. U.S. Pat. No. 5,155,137 (Keefer et al.) and U.S. Pat. No. 5,250, 550 (Keefer et al.) disclose complexes of nitric oxide: and polyamines. U.S. Pat. No. 5,389,675 (Christodoulou et al.) discloses mixed ligand metal complexes of nitric oxide-nucleophile adducts and U.S. Pat. No. 5,525,357 (Keefer et al.) and U.S. Pat. No. 5,405,919 (Keefer et al.) disclose polymer-bound nitric oxide/nucleophile adduct compositions. U.S. Pat. No. 4,954,526 (Keefer et al.; the '526 patent) and U.S. Pat. No. 5,212,204 (Keefer et al.) disclose the use of ionic diazeniumdiolates as cardiovascular agents. In addition, the '526 patent discloses O^2-substituted and metal-bound diazeniumdiolates. Keefer et al., U.S. Pat. No. 5,366, 997 ('997), discloses diazeniumdiolates having the formula:



in which the O^2-oxygen of the $N_2O_2^-$ group is bonded to the functional group R^3. When the R^3 group is cleaved from the O^2-oxygen, NO can be released spontaneously.

Although Keefer et al. ('997) discloses that (i) R^1 and R^2, together with the nitrogen atom to which they are bonded, can form a pyrrolidinyl, piperazino or other heterocyclic group, (ii) R^3 is a C_{1-12} straight-chain or C_{3-12} branched-chain alkyl, optionally olefinic and/or substituted with hydroxy, halo, acyloxy or alkoxy, a C_{1-12} unsubstituted/substituted acyl, sulfonyl, carboxamido, sulfinyl, sulfenyl, a carbonate derivative or a carbamate derivative, and (iii) the pyrrolidinyl group can have the structure:



wherein w=4, and R^4=hydrogen, a C_{1-8} straight or branched chain alkyl, a C_{3-8} cycloalkyl, or a substituted or an unsubstituted aryl, Keefer et al. ('997) does not disclose that R^3 is an aryl or a substituted aryl or that the pyrrolidino group can be substituted with a substituted or unsubstituted carboxyl group (see, also, Example 1 of U.S. Pat. No. 5,632,981) at position 2. Similarly, Keefer et al. ('997) does not disclose O^2-glycosylation of diazeniumdiolates.

Heretofore it was not known that O^2-aryl substitutions of the diazeniumdiolates was possible. Further, chemical studies of previously disclosed diazeniumdiolates led to the conclusion that they are generally at least as stable at high pH as they are at low pH, and that, unlike certain other classes of "nitrovasodilator" drugs, their rates of NO release are not affected by the presence of nucleophilic thiols.

Thus, there remains a need for such classes of diazeniumdiolates, which offer advantages over other currently available diazeniumdiolates. In this regard, the O^2-aryl substituted diazeniumdiolates are advantageous in that they can release NO spontaneously under alkaline conditions or after nucleophilic attack. O^2-Aryl substituted diazeniumdiolates also can release NO spontaneously after a combination of oxidative or electophilic activation and nucleophilic attack.

It is, therefore, a principal object of the present invention to provide a nitric oxide/nucleophile adduct in which the O^2-oxygen of the N_2O_2– group is derivatized with an aryl or substituted aryl group to protect the diazeniumdiolate against the spontaneous release of NO. It is another object of the invention to provide a novel class of diazeniumdiolates, which resists releasing nitric oxide in neutral or acidic solutions, but releases NO on nucleophilic attack or on increasing the pH. It is still another object of the present invention to provide O^2-glycosylated 1-substituted diazen-1-ium-1,2-diolates and O^2-substituted 1-[(2-carboxylato) pyrrolidin-1-yl]diazen-1-ium-1,2-diolates. It is a further object of the present invention to provide compositions comprising such compounds, including compositions comprising a nitric oxide/nucleophile adduct comprising a novel targeting moiety. It is a related object to provide O^2-aryl substituted diazeniumdiolates, which are amenable to bio-